REMARKS

Claims 23-26, 28, 30-33, 35, and 37-43 are currently under consideration. The amendments to Claim 23 are supported at least at page 15, lines 6-8 and 16-17. The amendments are also supported at least at example 10 and Table 2, where DNA, PEI, and modified PEI were all formulated in 8% glucose, and that for the transcutaneous method, DNA formulated with sugar only was the most efficient gene delivery system. The Applicants have pointed out that these claims are founded on several distinguishable improvements included in the text of this application: improved transfection rates of antigen presenting cells *in vitro* using a material newly introduced in the gene therapy field by others (PEI), so that a CTL response could be obtained in vitro, a chemical modification of PEI to adapt it better to the Applicants' field of interest, immune therapy, development of alternatives to the chemical modification, including an elegantly simple, inexpensive modification, and a method of needless vaccination.

Priority

The Examiner has acknowledged that this case is a division of the parent patent, and states that the claims are patentably distinct from the parent patent.

Specification

The Examiner states that the amendment to the first line of the specification filed 6-7-04 has omitted original text, i.e. reference to "USSN 09/153,198" has been deleted completely without being marked as being deleted. The correct format for the first line is as follows: "This application is a division of US Application 09/153,198, filed 9-15-98, now US Patent 6,420,176, which is a continuation-in-part of...." It is noted that the instant application appears to be a ClP and not a DIV of '198.

The Examiner states the status of the application on pg 9, line 7, will have to be updated as necessary.

The status of the application on pg 13, line 36, will need updated as necessary.

The status of the application on pg 18, line 32, *will* need updated as necessary.

Response

The specification has been amended as required by the Examiner, and the status updates will be provided upon a change in status.

Claim Rejections – 35 USC § 112

1. Written Description.

Claims 37-39 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

The Examiner states that Claims 37-39 remain rejected under written description because the specification does not describe the structure of the gene delivery complex capable of transfecting APCs such that a therapeutic or prophylactic effect is obtained - the sole disclosed purpose for transfecting APCs disclosed in the specification. Claims 37-39 require applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding a protein from HIV (37), from a replication-defective HIV (38), or an integration-defective, replication-defective HIV (39). The only described function for such a method is to treat or prevent HIV infection. The specification does not provide adequate written description for applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding a in HIV protein such that a therapeutic or prophylactic effect is obtained.

The Examiner admits that the Applicants describe plasmids encoding replication-defective, integrase-defective retroviral DNA in related application 08/989,301 as being non-lethal and capable of inducing a therapeutic/prophylactic immune response when administered *in vivo*. However, the Examiner cites a prior art reference, Adachi, of record (J. Virol., Aug. 1986, Vol. 59, pg 284-291), which taught such viruses were still infectious. The Examiner states that the Applicants do not adequately describe DNA encoding a HIV protein that is capable of inducing a therapeutic/prophylactic immune response. Nowhere have applicants provided any evidence that the amount of expression of viral protein is adequate to induce a therapeutic/prophylactic immune response or that the virus does not replicate too much and cause disease.

The Examiner states, without citation, that use of the plasmids encoding replication-defective retrovirus in animals as claimed would not treat or prevent disease because the virus would replicate and cause disease. The Examiner states that the Applicants appear to be attempting to find DNA comprising a lentiviral protein that expresses adequate viral protein such that a cellular immune response can be obtained, wherein said DNA i) does not make retroviral particles or ii) does make viral particles that replicate to a low degree without causing disease. Naming a type of material that may exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming a method of using DNA encoding replication-defective retroviral proteins without defining the DNA that will encode adequate amounts of retroviral protein to induce a therapeutic/prophylactic effect without causing retroviral particle formation or retroviral infection is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)).

The Examiner admits that the specification suggests using the method claimed to induce an immune response in a mammal (pg 20, Example 4). However, the Examiner argues that Example 4 does not correlate to the claimed invention because dendritic cells were transfected in vitro and because the gene delivery complex was not applied to the skin or mucosa as claimed. The Examiner states that merely inducing an immune response in a mammal by administering transfected dendritic cells, in and of itself, does not have a function by itself in Example 4 without inducing an immune response as described on (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response according to the

specification must result in a therapeutic or prophylactic effect to meet the description of the invention in the application as originally filed.

Therefore, the specification does not provide adequate written description for applying a gene delivery complex to the skin or mucosa of an animal, wherein the gene delivery complex comprises DNA encoding an HIV protein such that a therapeutic or prophylactic effect is obtained.

Applicants argue, "the present language is supported on pg 13, lines 27-36" (pg 8 of response). Applicants' argument is not persuasive. Pg 13, lines 27-36, does not address the written description rejections above because it generically relates to DNA encoding a replication or integration defective HIV virus.

Applicants' arguments regarding the case law on pg 8 of response are moot because the case law cited relates to enablement and not written description.

Response – Written Description

A. Therapeutic Effect/Correlation of Experiments

It is noted that Claims 23-26, 28, 30-33, 35 and 40-43 are not subject to this rejection. The rejected Claims all depend from Claim 23, which meets the written description requirement, as explicitly acknowledged by the Examiner. Thus the question is whether there is adequate support in the specification for the added limitations relating to the use of specific materials in the claimed method.

The Claimed invention is:

A method of transfecting antigen presenting cells, the steps comprising

selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter. This method is acknowledged to find support in the application. The question raised by the Examiner is whether the specification supports the further limitations, wherein the protein is from a human immunodeficiency virus (Claim 37); that is replication-defective (38); by virtue of being integration-defective.

1. The Claim Language was approved in the Parent Application.

It is further noted that the present application is a division of USPN 6,420,176, re Composition for Delivering DNA into Antigen Presenting Cells, which has the same specification as the present application, and includes the following dependent Claims:

> 3. The gene delivery complex of Claim 2, wherein the reverse transcriptase-dependent virus is a human immunodeficiency virus.

4. The gene delivery complex of Claim 3, wherein the human immunodeficiency virus is replication-defective.
5. The gene delivery complex of claim 3, wherein the human immunodeficiency virus is integration-defective.

In an effort to expedite prosecution, the limitations with respect to the material used in the present claimed method were made to quote those of the parent patent. Similar limitations are also found in the parent case, at Claims 11-13. The Applicants note that the issues involving written description and enablement were raised by the Examiner during prosecution of the parent patent and resolved at that time. The Applicants have a right to uniform application of the patentability standard (MPEP 706). Piecemeal Examination is to be avoided (MPEP 707.07). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706).

The Examiner has admitted that the claimed method meets the written description and enablement requirements, and the objections with respect to written description and enablement relate to language that was considered and allowed in the parent patent.

2. The Claimed Material was used in an Experiment in the Application, and produced a Therapeutic Result, which has been confirmed by Subsequent, Peer-Reviewed Publication.

The claimed function of the method is to transfect antigen presenting cells. The Examiner has acknowledged that transfection of antigen presenting cells has been demonstrated. The Examiner has made a requirement for a further showing of a therapeutic or prophylactic effect using a subset of materials. The Applicants have pointed to Example 4, page 20, which discloses that an immune response, that is, a CTL response, had been obtained in at least one animal after a single immunization attempt, using a LW/Int- plasmid (disclosed at page 18, lines 30-31 as a plasmid DNA encoding an integration and replication defective HIV). That immune response is evidence that the claimed effect, transfection of antigen presenting cells, has been achieved, and further that the stated purpose of transfection, to raise an immune (CTL) response, has been achieved. The application discloses that CTL responses are associated with therapeutic effects at page 4, lines 7-11: "Expression of foreign genes in antigen presenting cells (APC) may be used to generate efficient CTL response in animals. Therefore, gene transfer and genetic modification of

APC has the potential to generate effective vaccine and therapeutic approaches ...." That is, generation of a CTL response is a legitimate marker for a therapeutic effect.

The Examiner states that Example 4 does not correlate with the claimed invention, however, because Example 4 does not use the claimed method of delivery of genes through the skin. However, the Applicants point out that Example 4 was included to show efficacy of the claimed materials in a more classical method, such as described in USSN 08/803,484. The application discloses in the discussion at the end of Example 9 that

> These experiments show that PEI-(Man)-DNA complexes are able to penetrate in the skin, and deliver the DNA into Langerhans cells. The Langerhans cells were activated and migrated into the draining LN and expressed genes encoded by the DNA construct in the LN. It is known that cultured DC reinjected to the body migrate in the LN and generate efficient immune response. This invention demonstrates that in vitro isolation of DC is not required to transfer genes into Langerhans cells, or for gene expression in the lymphoid organs. We have also demonstrated that expression of a replication defective virus in DC results in efficient induction of a CTL response in vitro and in vivo (see above *sic*: This is a reference to Example 4). Therefore, we have shown that transcutaneous gene delivery with complexes (like PEI-man-DNA) can be utilized to generate immune responses against proteins encoded in the DNA.

Further, the Applicants have submitted an article by the inventors from a peer-reviewed journal, Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/Aids" J Invest Dermatol, 2004 detailing the use of the present invention to produce CTL responses. That article begins as follows:

> "One strategy for a new immunotherapeutic intervention against human immunodeficiency virus (HIV) infection is to develop a vaccine that can reconstitute HIV-specific immunity, thereby improving the efficacy of the present antiretroviral regimens. The therapeutic efficacy of such a vaccine would be mediated by HIV-specific T cells...."

This article is consistent with the teachings of the present application, and its acceptance for publication is some evidence that others of skill in the relevant art agree with the inventors that the CTL response is an acceptable marker for a therapeutic response. This article also includes a detailed discussion of a comparison between the immune responses raised via topical immunization and *ex vivo* immunization. The entire discussion revolves around T cell responses. See page 6, Col. 1. The authors conclude at page 7, first full paragraph, lines 1-3 that "We have shown here in a primate model that topical DermaVir vaccination is comparable with *ex vivo* DC-based vaccination." This article confirms the results disclosed in the present application, and is some evidence that those of skill in the art accept the results shown in the present application.

Example 4 demonstrates the efficacy of the claimed materials in the *ex vivo* method; the other examples demonstrate that the topical method works as well as or better than, the

ex vivo method for very similar materials, except that a marker gene is used, the discussion in the disclosure ties the two materials together, and the subsequent publications demonstrate that the disclosure in the application is acceptable for publication in a peer-reviewed journal.

B. Fine-tuned DNA

The Examiner is requiring the disclosure of a specific DNA structure, apparently on the assumption that the present invention relates to a detailed search for a specific class of materials. The invention relating to a class of materials, and the *ex vivo* method of using that class, is the subject of a distinct patent application by the inventors, USSN 08/989,301. The present discussion from the Examiner (at page 7, last paragraph) confuses viral particles, which in the case of HIV are RNA, and the claimed DNA, which comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter.

In USSN 08/989,301, the applicants described plasmids that are DNA encoding genes from a replication-defective, integrase-defective retrovirus. These plasmids are not retroviral particles. They are chemically different from viral particles, DNA, not RNA, and the difference is significant in the context of this invention. The DNA is non-lethal and capable of inducing a therapeutic/prophylactic immune response when administered *in vivo*. The corresponding viral particles (in the particularly difficult case of HIV), however, are disclosed to be either ineffective to raise an immune response or too dangerous to use. (USSN 08/989,301 page 3, lines 17-22).

The applicants proved up their disclosure from USSN 08/989,301 at least in another article by the inventors of record, Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells" J Virol, Aug 2001, p. 7621-7628.

That article contains Fig. 1 (b-d) comparing attempts to infect human lymphocytes (b) macrophages (c) and DC (d). The researchers noted that "In contrast to the parental wild-type virus (LW), the integrase-mutant virus was unable to produce productive infection in primary human cells." See also the discussion at the first partial paragraph of 7623, col. 1, lines 7-12, where this inability to produce protein is said to confirm that the viral particle is replication-defective. The article also discloses that "To circumvent the problem of viral vector expression in the absence of integration, we introduced the HIV-1 vector into DC as plasmid DNA" 7623, col. 2, first full para, lines 2-4. Fig. 2(b) compares p24 production (a marker for gene expression) for the wild-type virus, plasmid carrying the integrase-defective mutant, and a control plasmid with a marker gene. The plasmid did express p24 protein in an amount comparable to that of the wild-type virus.

With the distinction between the DNA and viral particles in mind, is it is clear that the inventors have demonstrated both a theoretical base and practical result where plasmids encoding replication-defective retrovirus can express protein whereas the corresponding viral particles cannot.

2. Enablement

Claims 37-39 remain rejected under 35 U. S.C. 112, first paragraph, because they are said to contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

Claims 37-39 are said not to be enabled because the specification does not provide adequate guidance for one of skill to induce a therapeutic or prophylactic immune response by applying a gene delivery complex encoding HIV to the skin or mucosa of an animal.

Claims 37-39 are said to require applying a gene delivery complex to the skin or mucosa of an animal, wherein the complex comprises i) DNA encoding an immunogenic protein operably linked to a promoter; and ii) sugar, polyethylenimine (PEI), a PEI derivative, wherein the protein is from HIV (37), a replication-defective HIV (38), or an integrationdefective, replication-defective HIV (39).

The specification is admitted to describe using the method claimed to induce an immune response in a mammal (pg 20, Example 4). However, the Examiner takes the position that merely inducing an immune response in a mammal, in and of itself, does not have an enabled use because inducing an immune response is only described in the specification as being used to obtain a therapeutic or prophylactic effect (pg 2, lines 20-24; pg 18, lines 2-8). Therefore, inducing an immune response against HIV according to the specification must result in a therapeutic or prophylactic effect to have an enabled use. The ordinary artisan reading claims 37-39 in view of the specification would determine that the methods were only used for therapy or prophylaxis. Enablement rejection b) is based on the sole disclosed use for the methods of claims 37-39 - therapy or prophylaxis.

The Examiner comments that Klatzmann and Sticker taught retroviral vaccines have been unable to protect against infection (Klatzmann, US Patent 6,140,114, Oct. 31, 2000; Stricker, Medical Hypotheses, June 1997, Vol. 48, pg 527-9, both of record). Overall, a lack of understanding about protective immunity to retroviruses such as HIV, the sequence variability and the rapid replication of retroviruses contribute the ineffectiveness of vaccines against retroviruses (Bangham, of record, Nov. 29, 1997, Lancet, Vol. 350, pg 1617-1621; pg 1617, top of col. 1).

The Examiner admits that the specification teaches making plasmids encoding replication defective, integrase-defective HIV as described in application 08/989,301 (pg 18, line 30-32). In application 08/939,301, applicants call such retroviruses "Class 4" viruses that are infectious but replication-defective (pg 15, lines 1-5). In application 08/989301, applicants teach that replication defective HIV that does not replicate effectively is inadequate to elicit a protective cellular immune response. Alternatively, replication defective HIV that does replicate effectively causes disease and sometimes fatal (pg 3, line 17 through pg 4, line 3). The Examiner states that the amount of replication of a retrovirus required to obtain a therapeutic cellular immune response without causing disease was unknown in the art at the time of filing. It was also unknown how to make a retrovirus with the adequate amount of replication that would provide an adequate cellular immune response without causing

disease. Without being able to make such a retrovirus, it was unknown how to use such a virus to obtain a therapeutic or prophylactic cellular immune response in a host.

The Examiner states that the specification does not provide adequate guidance regarding how to obtain a therapeutic or prophylactic effect by applying a replication defective retrovirus in an animal as claimed. The specification does not teach the amount of a cellular immune response that is therapeutic or prophylactic effect against a replication defective retrovirus. The amount of dendritic cells required to obtain adequate antigen presentation is not provided in the specification. The amount of retroviral protein expression required to obtain the desired cellular immune response is not provided in the specification. The amount of replication and infectiousness required to obtain the desired balance between therapy and pathogenicity is not provided in the specification. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine how to make and/or use a replication defective retrovirus to obtain a therapeutic/prophylactic effect without causing disease or death.

The Examiner states that, in addition, it was unpredictable what vector, promoter, dosage, cells, level of expression and route of administration would provide a therapeutic or prophylactic effect using in vivo or ex vivo gene therapy (Miller 1995, FASEB J., Vol. 9, pg 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶, pg 65, 1st ¶ under Conclusion section; Verma, Sept. 1997, Nature, Vol. 389, pg 239-242; see entire article, specifically pg 240, sentence bridging col. 2 and 3; Crystal, 1995, Science, Vol. 270, pg 404-410, pg 409; Ross, Sept. 1996, Human Gene Therapy, Vol. 7, pg 1781-1790; pg 1782, col. 2, 1st full ¶; pg 1789, col. 1, 18t ¶, all of record).

Response

This application includes information about multiple non-viral delivery vectors (the claimed complex comprising DNA and one or more compounds selected from the group consisting of sugars, PEI and PEI derivatives, and the experiments contain a clear description of the materials that were used, including the promoters (Example 1, page 19, line 9 and Example 2, page 19 line 18). Level of expression is reported in Example 1 page 19, lines 3-10, Example 2, lines 21-22, Example 3, Fig. 5 (as CTL in vivo response), Example 5 line 26, Example 6, Table 1, Example 7, lines 23-26, Example 8, Table 2. Different routes of administration were used in Example 4 (injection) and Example 8 (topical).

The specification is said not to enable applying DNA encoding a lentiviral protein to the skin or mucosa to transfect APCs and obtain a therapeutic or prophylactic effect. It is said that the specification does not teach that applying DNA to the mucosa results transfection of APCs or in expression of the protein in the APCs. It is said the specification does not teach the amount of lentiviral protein expression required for the APCs to present adequate antigens to the immune system such that a therapuetic/prophylactic immune response is obtained. It is said the specification does not teach the immune response to a lentiviral antigen required to treat or prevent disease. It is said the specification does not provide the combination of vector, promoter, dosage, level of expression that would result in a therapeutic/prophylactic effect. Given the teachings in the specification taken with the unpredictability in the art at the time of filing, it would have required one of skill in the art at the time of filing undue experimentation to determine the vector, promoter, cell, dosage, level

of expression and route of administration required to obtain a therapeutic or prophylactic effect using the method claimed.

The Examiner comments that the Applicants argue the Examiner has not correctly stated the applicable law, but applicants have not pointed to any specific error. Applicants imply the Examiner has attempted to evade the instruction received from the Federal Circuit, but the case law cited by applicants does not apply. Applicants' arguments are not persuasive because the examiner has cited the law under 112/1st paragraph regarding enablement and has addressed all standards for enablement (i.e. the Wands factors, the state of the art, the skill level of those in the art) discussed in case law relating to enablement.

Applicants argue that the Examiner's interpretation of the claimed invention as being limited to a method of transfection APCs by applying the complex to the skin or mucosa of an animal for the purpose of therapy or prophylaxis is in error because the claims merely require transfecting APCs and do not require a step in which therapy or prophylaxis is obtained. Applicants' argument remains unpersuasive. The claims must be read in light of the specification. The only purpose for applying DNA encoding an immunogenic protein to the skin or mucosa of an animal is for therapy or prophylaxis. Pg 13, lines 19-25, states:

"If the purpose of the gene transfer is to induce an immune response, then the genetic material must express one or more immunogenic proteins. Transduced cells will subsequently express enough of the immunogenic proteins (different viral antigens and produce authentic enough viral particles) to provoke a sufficient immune response (e.g., protect the individual from infection by the wild-type virus)."

When reading the claims in light of the specification, merely applying DNA encoding an immunogenic protein to the skin or mucosa of an animal (or even adding the optional phrase "transfecting APCs" in the preamble) without obtaining a therapeutic or prophylactic effect does not have a disclosed or enabled use and has no meaning. Therefore, it is reasonable to interpret the claimed methods as only being used for treatment or prophylaxis and to determine whether applicants have provided adequate guidance for that one disclosed use, i.e. whether applicants provide adequate guidance for those skilled in the art to apply DNA encoding an immunogenic protein to the skin or mucosa of an animal and obtain therapy or prophylaxis. As Such, the method claims (having only one disclosed use without specifically reciting the one disclosed) remain rejected under enablement because their one disclosed use has not been enabled.

The Examiner says the Applicants argue the in vitro data described by applicants enables the invention, but that the Applicants' argument is not persuasive. The claims require applying the complex to the skin or mucosa of an animal; therefore, the claims are limited to transfecting cells *in vivo*. The *in vitro* data does not correlate to *in vivo* data for reasons cited above because the only disclosed use for performing the method *in vivo* is to obtain an immune response against the immunogenic protein that is therapuetic or prophylactic. However, HIV patients have a CTL response to HIV proteins that is not therapeutic or prophylactic. Furthermore, the immune response required to treat or prevent lentiviral infection was not known (see references of record above). Thus, the art was and continues to be completely absence of methods to treat or prevent lentiviral infection in vivo using by inducing an immune response. Therefore, data showing that APCs can be transfected in vitro using a gene delivery complex as claimed cannot support using the claimed method to treat or prevent disease.

Applicants argue the *in vivo* data described by applicants enables the invention. Applicants provide Lisziewicz (J. Invest. Derm., Jan. 2005, Vol. 124, No. 1, pg 160-169 (which is equivalent to the Lisziewicz, 2004, reference provided by applicants, but not found

elsewhere)) who taught using DermaVir to make particles containing DNA, PElm and glucose and administering the comlex on about 40 cm2 skin at four locations: the left and right upper inguinal region and left and right axialliary region for 30 minutes (pg 167, col. 1, "Topical and ex vivo DermaVir immunization"). Applicants argument is not persuasive.

DermaVir, described in Lisziewicz (2005) is not disclosed in the instant application. The structure of DermaVir is not described by Lisziewicz (2005) but is "formulated to make a approximately 100 nm particle containing DNA, PElm, and glucose" (pg 167, col. 1, "Topical and ex vivo DermaVir Immunization" of Lisziewicz (2005)). Lisziewicz (2005) states DermaVir was used in Lisziewicz (2001, of record); however, Lisziewicz (2001) described using PEI or PEI-mannose to deliver DNA (at a 5:1 ratio) without using glucose. Thus, DermaVir, mentioned by Lisziewicz.in 2005, was used to make gene delivery particles containing DNA, PElm and glucose; however, the structure of DermaVir was not described in Lisziewicz (2005). Therefore, the gene delivery complex described by Lisziewicz (2005) does not correlate to the instant application because it teaches more than the original disclosure (DermaVir). The instant application does not describe the structure of DermaVir which may be essential to the invention. As such, Lisziewicz (2005) cannot be relied upon for enablement of the instant application because it uses DermaVir, which was not disclosed in the instant application.

Furthermore, Lisziewicz (2005) is limited to particles containing plasmid DNA, PEI-mannose and glucose (pg 166, col. 2, 1st full para), which is. much narrower than the claimed invention. Therefore, the limited species of gene complex of Lisziewicz (2005) cannot be relied upon for enablement of the broader genus of gene delivery complex used in the method of claim 23.

Finally, Lisziewicz (2005) does not enable one of skill to use the gene delivery complex to obtain a therapeutic or prophylactic effect. Inducing an HIV-specific immune response in vivo against a lentiviral protein failed to provide a therapeutic or prophylactic effect (Lori, Current Medical and Chemical Anti-infective Agents, 2004, Vol. 3, pg 31-41; pg 31, col. 1, 2 nd %, lines 7-10). Ready (Nature Medicine, (April 2003, Vol. 9, No. 4, pg 376) clearly states that H IV vaccines capable of preventing infections in humans was not predictable (col. 1, last full T) and that the road to such a vaccine "is littered with abandoned candidates" (col. 1, last 4 lines). Applicants have not provided any evidence or any reasonable explanation that the claimed method overcomes such unpredictability so that an adequate immune response would be induced and a therapeutic or prophylactic effect obtained. Without such guidance, inducing CD4 helper and CD8 cells as described by Lisziewicz (2005) is not adequate to enable using the claimed invention to obtain a therapeutic or prophylactic effect.

The examiner is not requiring a showing or exemplification of inducing a therapuetic or prophylactic immune response using the method claimed; rather, the examiner is requiring a showing or exemplification of inducing a therapeutic or prophylactic immune response using the method claimed or a reasonable teaching of how to overcome the unpredictability in the art, i.e. the amount and type of protein to be expressed, the combination of promoter, protein and vector required to obtain adequate amounts of protein expression upon being applied to the skin or mucosa, how to adequately target the proper number of APCs by applying DNA to the skin or mucosa, the proper number of APCs to be targeted and the immune response required to treat or prevent lentiviral infection. In this case, applicants have provided neither a showing or a reasonable correlation.

Applicants arguments regarding Animal Legal Defense Fund vs Quigg, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985) (pg 6 and pg 12 of response) are moot because the case relates to

utility under 101 and not enablement. The case law also relates to animals and not to methods of applying a DNA complex to an animal as claimed in the instant application.

Applicants arguments regading Radomex vs Scopus Corp. (pg 6 and pg 12 of response) are also moot because the examiner has taken the level of skill into account throughout the enablement rejection.

Applicants argument regarding Lindeman Maschinenfabrik GmbH v American Hoist & Derrick Co. is misplaced because it relates to establishing what was known at the time of filing. The examiner has provided numerous references regarding what was known about using HIV vaccines to treat or prevent disease.

Applicants cite other case law on pg 7 and 12 of the response but fail to correlate the case law to the claimed invention. The case law on pg 7 and 12 has been reviewed but is misplaced because they relate to 101 rejections and to Wands factors that have been specifically addressed by the examiner.

Again, applicants erroneously state the examiner is requiring a showing of a therapeutic or prophylactic effect (pg 7, 1 st full ¶). Instead, the examiner is requiring either a showing of a therapeutic or prophylactic effect or a reasonable teaching so that one of skill would be able to overcome the art established unpredictability that persists to this day. Neither has been fulfilled in this case.

Applicants state "Klatzmann and Stickler relate to retroviral vaccines (not DNA) of others in totally different methods of gene delivery, and demonstrated failure of others" (pg 13, lines 1-8 of response). Applicants' argument cannot be determined. The Klatzmann and Stickler establishes that the lack of understanding about protective immunity to retroviruses such as HIV, the sequence variability and the rapid replication of retroviruses contribute the ineffectiveness of vaccines against retroviruses. As such, Klatzmann and Stickler establish that treating or preventing HIV using a vaccine - even DNA encoding an HIV protein as claimed -requires knowledge of the protective immunity required to treat or prevent HIV or to overcome the sequence variability of HIV. Therefore, the teachings of Klatzmann and Stickler clearly relate to any composition used to treat or prevent HIV infection. Applicants fail to overcome the teachings of Klatzmann and Stickler, both of record, and Lori and Ready, both provided in the instant office action, by teaching the protective immunity required to treat or prevent HIV or how to adapt the method to the sequence variability of HIV.

Response – Enablement

The applicants note that the present rejection lies against Claims 37-39. Claims 23-26, 28, 30-33, 35 and 40-43 are admittedly enabled. This is essentially the same rejection as the Written Description rejection above, and many of the same arguments apply. For the sake of brevity and clarity, the argument with respect to written description above has been limited to the extent possible to the underlying facts. That is, to a discussion of the words and evidence relating to the Written Description requirement. In sum, the Applicants have, above, pointed out that the Claims are supported by specific teachings in the application text and by experimental results, and the teachings of the application have been confirmed by subsequent work of both the authors and others. The teachings of the application have been

accepted by peer-reviewed journals. What follows is a discussion of the law applicable to the legal question of enablement, and an analysis of the law applied to the present case.

A. Applicable law: 35 USC § 101 and § 112 – Utility, Enablement, Written Description

The Examiner has stated that the Applicants have not cited applicable or controlling law. The statement of law previously supplied is correct, and is incorporated here by reference. The controlling case law remains *In re Brana*, 51 F.3d 1560, 34 USPQ 2d 1436 (Fed. Cir. 1995), where the Federal Circuit reversed a decision by the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board) affirming an Examiner's rejections of claims to antitumor compounds for failure to comply with 35 USC §112, 1st ¶.

In re Brana was decided in 1995. At the time the Federal Circuit observed that the question of what an applicant must prove with respect to the utility of pharmaceutical preparations had been settled by the case law, citing cases in its predecessor court that went back to 1961 (*id* at 51 F.3d 1560, 1564). The Court also noted that the utility requirement is found in 35 USC § 101, but that the requirement is subsumed in the written description requirement (*id*). This means that when the issue of utility is involved, cases decided under the headings "written description," "enablement," "utility," 35 USC § 101, and 35 USC § 112 may be relevant, and certainly cannot be distinguished on the basis of the heading alone.

One of the issues in the *In re Brana* case was whether the applicants proved the claimed compounds useful (*id*, at 1566). That is, whether the tests offered by the applicants to prove utility were inadequate to convince one of ordinary skill in the art that the claimed compounds were useful as antitumor agents. The Applicants had pointed to language in the application, and *in vitro* data in the application. The Examiner had pointed to journal articles discussing the therapeutic predictive value of *in vivo* murine tests. The Applicants pointed to a Declaration filed during prosecution with *in vivo* animal data (murine models).

The Court ruled that *the applicants should not have been required to substantiate their presumptively correct disclosure* to avoid a rejection under the first paragraph of § 112, and that the later-filed Declaration was available to prove assertions made in the patent application (*id* at 1567).

The Court specifically addressed the question of whether animal models can be used to demonstrate utility, and commented as follows: "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful

contribution to the art, even though it may eventually appear that the compound is without value in the treatment in humans." *id* at 1567.

Given the clear, direct, and on-point teachings of this case, the next question is whether the applicable law has changed since 1995. The *Brana* case has not been reversed. Indeed, the opinion in the *Brana* case is wholly consistent with the current Examining Guidelines, because both the opinion and the Guidelines cite *In re Marzocchi*, 439 F.2d 220, 223, 169 USP 367, 369 (CCPA 1971) for the same point:

> 2-Burden on the Examiner - MPEP 2164.04 and In re Brana 51 F2d.3d 1560, 1566:
>
> The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. If an examiner can provide reasons sufficient to create a reasonable doubt as to the accuracy of a particular broad statement put forward by applicant as enabling support for a claim, a rejection under 35 U.S.C. 112, first paragraph can be made. A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. Citation omitted.

The Examiner contends that he has cited the *Wands* factors, which are used to allegedly support a demand for disclosure about retroviral vectors, including the amount of replication of a hypothetical retrovirus, and how to get a therapeutic effect against that retrovirus, as well as vector, promoter, dosage, cells level of expressionand route of administration that others have said would be required in another field of endeavor, gene therapy. These are not *Wands* factors.

Wands factors are a list of factors that are to be considered in determining whether or not the experimentation required is undue under MPEP 2164.01: "(1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) presence of absence of a working example; (4) nature of the invention; (5) the state of the prior art; (6) the relative skills of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims." The *Wands* factors do not apply where the application text contains pertinent experimental results.

In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988) cannot override the later-decided, more-closely-in-point *In re Brana* (Fed. Cir. 1995). Moreover, the *Wands*

case does not stand for the proposition that the Applicants in the present case must conform their disclosure to any reference from the prior art. Indeed, in *Wands* the Federal Circuit reversed a Board finding of non-enablement, and the case stands instead for the proposition that a verbal description of how to obtain micro-organisms that requires only methods known in the art and routine screening, can be enabling, without regard to any deposit requirement.

It is abundantly clear from this case law that experimental results in an animal model, including *in vitro* results using cell lines, (*In re Brana*, at 1567) are acceptable to meet the utility/disclosure requirement under 35 USC 101 and 112, 1st ¶ skeptical journal articles notwithstanding (*id*, at 1566 and 1568).

B. Application of the Applicable Law to the Current Application.

Under the cited law, both the case law and the Examination Guidelines, where a specification disclosure contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, the disclosure must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein. So, the burden is on the Examiner to show that there is some basis to disbelieve the disclosure with respect to the material described in sub-claims 37-39. Such a rejection can be overcome by pointing to experimental results, which may be *in vitro*, and may be supplied after the file date, provided the new data supports the existing disclosure. In this case, the base claim has admittedly been enabled, and the presently claimed material was disclosed in the application, claimed in the parent patent, and used in an Example in both the parent patent and the present application. This material is enabled by the text of the present application.

C. There is no basis to reject the teachings of this application.

It is the claimed invention that must be examined. The claimed invention is:

A method of transfecting antigen presenting cells, the steps comprising

selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,

and applying the complex to the skin or mucosa surfaces of an animal,

wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter. This method is acknowledged to be enabled by the application. The question raised by the Examiner is whether the specification enables the

dependent limitations, wherein the protein is from a human immunodeficiency virus (Claim 37); that is replication-defective (38); by virtue of being integration-defective (39). The Examiner has taken the position that it is insufficient to show that the method induces an immune response (Applicants point out that their burden is to show that the method transfects antigen presenting cells); that something further, a "therapeutic or prophylactic effect" must also be shown, or in the alternative, that certain journal articles, which are admittedly not relevant as prior art, must be "overcome" because those references make predictions as to what would be needed to produce a vaccine along the lines envisioned by others, or demonstrate failure of others.

The applicants note that they have pointed out, *supra*, that a replication-defective, integration-defective set of proteins derived from HIV was used in this application to induce an immune response *ex vivo*, to demonstrate the utility of the raw materials being used, that the new method, which is an alternative to the *ex vivo* procedure used in Example 4, was proven up with a marker gene, and that the text of the application at Example 9 discloses that this invention demonstrates that *in vitro* isolation of DC is not required to transfer genes into Langerhans cells, or for gene expression in the lymphoid organs. The raw material described in Claims 37-39 was used in several experiments in the text of the text of this application, and transfected cells *in vitro* and using the *ex vivo* procedure. Use of the raw material is enabled.

Further, the cited publications by the inventors are not mentioned for the purpose of providing enabling disclosure, but confirming the statements that are already in the application. For example, the application discloses that CTL responses are associated with therapeutic effects at page 4, lines 7-11: "Expression of foreign genes in antigen presenting cells (APC) may be used to generate efficient CTL response in animals. Therefore, gene transfer and genetic modification of APC has the potential to generate effective vaccine and therapeutic approaches ...." That is, the application discloses that generation of a CTL response is a legitimate marker for a therapeutic effect, and the peer-reviewed journal articles confirm that others agree with the inventors on this point.

The Examiner's comments about the state of the art at the time the application was filed are true to the extent that the field was unpredictable; however, it does not follow that this application must set forth whatever any prior art references predicted to be needed. This application sets forth the details of basic research into the physiological mechanisms of raising a CTL response, and discloses important and useful advances in new materials, a theoretical and practical basis for targeting antigen presenting cells, and a method of vaccination that does not require injection. It is not at all surprising that the disclosure of this application does not conform to that of the predictions in the prior art. The standard for

invention is that the subject matter is new, useful, and non-obvious. If the present invention were merely in the ambit of the prior art predictions, it would be properly rejected for being either not new, or obvious over the references currently cited.

The Examiner's comment that "it was also unknown how to make a retrovirus with the adequate amount of replication that would provide an adequate cellular immune response without causing disease" was and is, in the inventors' opinion, true. However, the present invention does not use a retrovirus with a finely-tuned reproductive capacity, as discussed above (at B. Fine-tuned DNA). In brief, a plasmid DNA encoding a replication defective, integrase-defective HIV is not the same thing as the corresponding viral particle, and the difference in the materials has been exploited by the inventors.

The Examiner's discussion of the experimental support offered by the Applicants does not consider the teachings of the application or the experiments as a whole. The *in vitro* data complements the *in vivo* data. The experimental support in the application must be taken as a whole, for what each experiment provides. The publications are cited to confirm the statements in the text of the application, and were never suggested to be separate, enabling disclosures.

The Examiner's criticism that the subsequent publications by the inventors contain experiments under a variety of conditions is inapt. For example , the Examiner makes much of the use of a tradename, DermaVir, in 2005 article that cited another article, Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Tye 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells" J Virol.(2001) pp 7621-7628. However, the referenced 2001 article discloses the construction of plasmid DNA encoding the replication-and integration-defective pLW/int- as the raw material in terms that clearly are acceptable to those of ordinary skill in the art. This is the material used in Example 1, page 18, line 31. According to the *Wands* case, this description is sufficient.

The Examiner's statement that the article by the inventors, Lori, et al., "Cellular Immunity and DNA vaccines for the treatment of HIV/AIDS Curr. Me. Chem. - Anti-Infective Agents, 3 (2004) pp 31-41, somehow renders the invention disclosed in this application unenabled because that article reports the failure of the first phase III HIV preventive vaccine trial (AIDSVAX B/B) is incorrect as a matter of law and as a matter of fact.

This kind of rejection has been considered, and found to be unacceptable. "We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may

eventually appear that the compound is without value in the treatment in humans." *In re Brana* at 1567, quoting *in re Krimmel* 292 F2d 953, 130 USPQ at 219.

In addition, the failure of that vaccine trial merely confirms the inventors' own disclosure of the need for other materials. AIDSVAX B/B is a subunit vaccine derived from the single protein gp120.

See http://www3.niaid.nih.gov/news/newsreleases/2002/phase3hiv.htm

AIDSVAXB/B had been part of a program involving a canary-pox based vaccine using a single protein, and then using the single protein as a subsequent boost (prime and boost) to produce antibodies. That trial demonstrates failure of others, and the result was predicted in another application by the present inventors, 08/803,404, at page 3, first paragraph where subunit vaccines directed to the production of an antibody response were disclosed to be problematic for HIV. The present inventors, in that application, proposed raising a different kind of immune response, using a different kind of material, that is, a method for raising a cellular immune response in a mammal, the steps comprising transducing antigen presenting cells selected from the group consisting of Langerhans cells, dendritic cells and mixtures thereof, with a plasmid DNA construct that encodes a replication-defective retrovirus, and exposing a mammalian host to the cells in a manner that allows the cells to express the construct in the lymphoid organs of the host, whereby a cellular immune response to the retrovirus is raised by the host. This is an alternative approach offered at a time when it was much needed, as confirmed by the Ready reference cited by the Examiner.

The Lori (2004) article does discuss the present invention: "our DC targeted HIV vaccine, DermaVir, a topical, therapeutic vaccine that has demonstrated immunological and clinical benefits in rhesus macaques" at page 32, Column 1, 1st full para, lines 1-5 *up*. The article presents pre-clinical studies, page 38-39, a theoretical basis to explain why the vaccine differs from other vaccines (page 39, 2nd full para) and a suggestion for its treatment as a new antiretroviral approach complementary to that of various drug classes (page 39, paragraph bridging Cols 1 and 2). This is by no means an indication that the material has no therapeutic value.

D. Conclusion – This Enablement Rejection must be withdrawn

The Examiner's requirement to show an effect beyond that of the claimed invention is legal error. The Examiner's alternative requirement that, in order for the presently claimed invention to be enabled, the text of the specification must show anything other than how one of skill in the art can make and use the claimed invention, that is, to include any number of items that those in the prior art or analogous art may have predicted would be

needed, is also legal error. The Applicants have properly stated the applicable law, which does indeed relate to the current rejection for alleged lack of enablement.

The Applicants recognize the difference between the Examiner and the USPTO, and think that responsibility for attempts to evade the settled law of the Federal Circuit rests with the USPTO, not the Examiner. Further, the applicants have a right to a clear and candid statement of the examination policy of the USPTO, which should be applicable to all art groups. If the USPTO has a policy try yet again to push for a ruling that clinical results will be required for medical inventions, or that prior art references can be used to determine the content of an application's disclosure, or that subsequent publications can "unenable" the disclosure in a patent application, then the applicants have a right to know this and have the policy opened up to public debate. The Applicants have reviewed the status of the applicable law relating to any requirement for data showing a "therapeutic or prophylactic effect" or in the alternative, a laundry list of requirements pulled from prior art documents, or any use of subsequent publications to "unenable" a disclosure, and cannot find them in the case law, MPEP, or Examiner's training materials.

A vaccine according to the currently claimed invention is in human clinical trials in two countries. It is noted that clinical trial results are expressly NOT required according to the MPEP, however, the MPEP also acknowledges that "Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. MPEP 2107.02.

A statement listing the trials can be found at
http://www.geneticimmunity.com/pages/906725/index.htm

Accordingly, in the event the current written description/enablement rejections are not withdrawn now, the Applicants renew their request for a written decision by the USPTO stating the legal basis for both of these requirements, and also a meeting with the Examiner's Supervisor and the Customer Service Specialist.

3. Indefiniteness

Claims 23-26, 28, 30-33, 35, 37-42 remain rejected and claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record. Claim 23 remains indefinite because the body of the claim merely requires applying a complex to the skin or mucosa surface of an animal but the preamble requires transduction of APCs. The body of the claim never obtains transfection of APCs or expression of the protein in APCs. Thus, the preamble and the body of the claim do not have a nexus making the claim as a whole unclear.

Claim 23 remains indefinite because it is unclear if "transfecting" is limited to transfection with plasmid or if the term encompasses infection with a viral particle. The specification does not define "transfection". Applicants argue the term was inserted "to comply with what they thought was a demand by the examiner." Applicants state they are open to suggestions but do not provide any suggestions or any other arguments. Applicants' arguments are not substantive. The examiner merely rejected the previous term "transducing" under 1 12/2nd in the office action of 3-10-04.

Claim 23 remains indefinite because the metes and bounds of what applicants consider "applying" to the skin cannot be determined. It is unclear if the phrase is limited to putting the complex on the skin or if the phrase encompasses subcutaneous injection which results in delivery of the complex under the skin. It is unclear if intravenous injection is encompassed by the phrase because such an injection does require contact of the complex to the skin when the injection passes through the skin. Applicants argue the phrase has support on pg "16, line 34, where application to the skin is distinguished from injection." Applicants' argument is not persuasive. Pg 16, line 34, merely states, "The complex can be applied to the skin or mucosa surfaces directly." The citation does not discuss injection or distinguish "applying" from "injecting."

Applicants' arguments do not address how to interpret the phrase. As such, one of skill would not be able to determine when they were infringing on the claim.

Claim 30 remains indefinite because the phrase and "method of claim 28, wherein the complex comprises a 5:1 ratio of polyethylenimine derivative nitrogen per DNA phosphate" is unclear. Claim 30 does not limit the complex to having polyethylenimine or polyethylenimine derivative; therefore, limiting the complex to having a 5:1 ratio of PEI nitrogen per DNA phosphate without first limiting the complex to one having PEI does not make sense because the complex can made with sugar (see claim 23). Furthermore, claim 30 refers to a 5:1 ratio of polyethylenimine derivative. It is unclear if applicants are attempting to limit the ratio or the compound used for gene delivery. Overall, the phrase is unclear.

Claim 31 remains indefinite because it is unclear whether the phrase "is formulated in a glucose solution" is limited to adding PEI, PEI-glu, PEI-gal, or PEI-man to a solution of glucose + water or if the phrase encompasses PEI-glu, PEI-gal, or PEIman + water. The specification teaches PEI may be glycosylated (pg 21, Table 1) or solubilized in glucose (pg 22, line 35). Overall, it is unclear whether the phrase is limited to PEI or PEI derivative added to glucose + water or if the phrase encompasses adding PEI-glu to water. Applicants' arguments relating to "unexpected results" are moot because they do not address the indefiniteness of the phrase. Applicants argue both scenarios described by the examiner are encompassed by the phrase; however, it is not clear that PEI-glu added to water is "formulated in a glucose solution" because the glucose may stay attached to the PEI and not solubilize into the water.

Response – Indefiniteness

The Applicants have a right to uniform application of the patentability standard (MPEP 706). Piecemeal Examination is to be avoided (MPEP 707.07(g)). Certain technical objections, (e.g., negative limitations, indefiniteness) should not be made where the examiner, recognizing the limitations of the English language, is not aware of an improved mode of definition. (MPEP 707.07(g)). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706).

The Applicants submitted a set of Claims that could have been allowed on the first office action in this case. The Applicants have, in good faith, used the text of the parent application's claims, and consulted with the Examiner to draft the present claims. Despite their own clear right to act as their own lexicographers, the Applicants have abandoned their original language in an effort to conform the claims to their invention to that favored by the Examiner, and repeatedly amended the claims for that purpose. The Applicants have pointed to support in the application and also asked, in writing, for a definite suggestion, as is their right under MPEP 706, and the Examiner has not responded. Accordingly, the Applicants respectfully request that, pursuant to MPEP 707(g), the present rejections be withdrawn because the Examiner is not aware of an improved mode of definition.

Claim Rejections - 35 USC § 102

4. Anticipation

Claims 23-26, 28, 30-32, 35, 37, 40 and 41 remain rejected and claim 43 is rejected under 35 U.S.C. 102(e) as being anticipated by Behr (US Patent 6,013,240, Jan. 11, 2000; 102(e) date=2-28-97) as supported by Carson (US Patent 5,679,647) for reasons of record.

Parent application 60/058,933 did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Therefore, claim 23 does not get priority back to parent application 60/058,933 (filed 9-15-97). Parent application 09/153,198 (filed 9-15-98) described complexing DNA with PEI-mannose in a 5-10% glucose solution on pg 26, lines 1-9. Therefore, claim 23 has priority to 9-15-98.

The Behr reference is said to have taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose Note: the stock solution was 5%, diluted twice (col. 12, lines 53-57). Luciferase is alleged, without citation to any evidence whatsoever, to be an immunogenic protein because it is foreign to mammals and induces an immune response in mammals. Behr is said to have taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr is said to have taught the DNA could encode an HIV peptide (col. 3, lines 57-67). The Examiner points to no teaching, but argues that the method of Behr inherently results in transfecting APCs because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3). While not relied upon for the basis of the rejection, Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). It is noted, however, the phrase "transfecting antigen presenting cells" in the preamble has not been deemed to have patentable weight in considering the art because the body of the claim does not require transfecting APCs.

Claims 25, 26 and 43 are said to be included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 are said to encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are said to be included because Behr taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral (11 bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are said to be included because administering the complex to the skin/mucosa as taught by Behr inherently would act activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

Applicants argue the luciferase gene is only a marker gene and is not used to raise or measure an immune response or transfect APCs. Applicants' argument is not persuasive. Luciferase is said to be an immunogenic protein as claimed because it is foreign to the animal to which the gene delivery complex is applied. Furthermore, the claims do not require inducing an immune response. The method of Behr inherently results in transfecting APCs because dendritic cells (a type of antigen presenting cell) are found in the epidermis (see definition of "dendritic cell", item 3).

Applicants argue Behr merely says the complex can be administered to the skin or mucosa without disclosing how to do so. Applicants' argument is not persuasive. Behr is said to have taught applying a gene delivery complex to the skin and need not demonstrate doing so to anticipate the claim. The step of applying the gene delivery complex in claim 23 has no limitation that distinguishes it from the step of applying taught by Behr.

Applicants argue the applicants have shown unexpected results and that Behr does not teach how to obtain a given result and only suggests performing a particular method. Applicants' arguments are not persuasive. The argument regarding unexpected results in misplaced under 102. Furthermore, the body of claim 23 does not require any given result that distinguishes it from the method taught by Behr. Finally, applying a gene delivery complex to the skin as taught by Behr inherently result in transfecting dendritic cells of the skin as supported by Carson.

Applicants argue the specification explicitly taught transfecting APCs. Applicants argue the phrase "transfecting antigen presenting cells" in the preamble of claim 23 should be given patentable weight because it "breaths life and meaning into the claim." Applicants argue the limitation "transfecting APCs" is directed to target cells having a specific function described on pg 11 and 12. Applicants' arguments are not persuasive.

The method of applying a gene delivery complex to the skin taught by Behr is alleged to inherently results in transfecting dendritic cells as supported by Carson.

Applicants' argument regarding changing the method of Behr so-as to render it inoperative has been considered (pg 18 of response). Applicants' argument is not persuasive. Behr is said to have taught applying a gene delivery complex to the skin of an animal. No changes to the step of applying are required, and the gene delivery complex taught by Behr is equivalent to the gene delivery complex in the method claimed.

Response – Anticipation

In their last response, the Applicants pointed out that the facts showing that the Examiner had failed to make a *prima facie* case under 35 USC § 102, including legal error for failing to point to all the limitations in the method claim within the four corners of the reference, and a factual error – the use of speculation, not evidence, to support an inherency argument, namely that the use of the marker gene, luciferase, demonstrated transfection of APCs and the inherent induction of an immune response in the Behr reference. That rejection should have been withdrawn in this Office Action, because the reference has been distinguished over.

The Applicants have a right to uniform application of the patentability standard (MPEP 706). Piecemeal Examination is to be avoided (MPEP 707.07(g)). Inventions relating to HIV/AIDS and cancer are specifically important, and suitable for expedited processing. (MPEP 708.02 X.) And, applications that are substantially allowable should be considered special and prompt action taken to require correction of formal matters (MPEP 1301). Even in ordinary cases, the Examiner should never overlook the importance of his or her role in allowing claims which properly define the invention (MPEP 706). The examiner's action should be constructive in nature and when possible should offer a definite suggestion for correction (MPEP 706).

In the event the present rejection is not withdrawn now, the Applicants request a written statement by the USPTO stating the legal basis for failing to withdraw a 35 USC §102 rejection where the limitations are not found within a single reference, and for maintaining an inherency argument where no evidence exists that the supposed results (immune response to luciferase) have been obtained.

A. Applicable Law – 35 USC 102

The Applicants note that the latest set of Examiner's Guidelines was modified in with respect to 102(e)(2), not relevant here, in 2000.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The **identical** invention must be **shown in as complete detail as is contained in the ... claim**. (emphasis added) The elements must be arranged as required by the claim. MPEP 2131. Multiple references may be used to (a) prove that a reference was an enabling disclosure, (b) explain the meaning of a term, or (c) show that a characteristic not disclosed in the reference is inherent (MPEP 2131.01). The burden is on the Examiner to first show that the claimed composition or machine is disclosed **identically** (emphasis added) by the reference, if an additional reference is to be used to show enablement (MPEP 2131.01 I.).

The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. (MPEP 2112.02)

The Behr Reference

The Behr reference relates to the use of PEI as an adjuvant for gene therapy, preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well. Gene therapy is disclosed to consist in correcting a deficiency or an abnormality (mutation, aberrant expression, and the like) or in effecting the expression of a protein of therapeutic value by introducing genetic information into the affected cell or organ (Col. 1, lines 11-15). Gene therapy is a field distinct from immunotherapy, and this reference discloses that immunogenicity, that is, the result obtained by the inventors, is to be avoided in this context.

The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), in a wide variety of configurations, including using a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57; sugars are listed as useful for targeting the asialoglycoprotein receptors at Col 5, lines 64-65), for a wide variety of purposes (for example, the production of therapeutic products including enzymes, blood derivatives, hormones, lymphokines,...growth factors, neurotransmitters...synthetic enzymes, etc,, -- a list that includes thousands of items. See Col. 3, lines 29-44. Antigenic peptides are also listed at Col. 3, line 57-67, as well as antisense genes (Col. 3, line 45), sequences (Col. 4, line 1, and upstream signals to control therapeutic genes (Col. 4, lines 25-29) and that it can be used in formulations with a view to topic, cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines

1-4) in formulations that that might be isotonic sterile solutions, dry, water or saline (Col. 6, lines 9-12 as appropriate *to enable injectable solutions to be formed* (line 13, emphasis added). Both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), but only direct injection is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration.

Among the differences between this reference and the presently claimed invention are that the reference does not disclose the targeting of antigen presenting cells, a most significant subset of cells, and prominent by its omission, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection.

The Carson Reference

Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). The definition of the complex is apparently plasmid DNA only, and is referred to repeatedly as "naked" (e.g., Col. 30, line 41). These materials were formulated in saline solution (Col. 31, line 18). Both of the cited experiments rely on devices: intradermal injection of plasmid (Example X, column 35, line48) or a tyne device (Col. 37, line 16). Naked DNA formulated in a glucose solution was tested in the Behr reference (Example 14, Col. 13, lines 9-10), and found not to work in that experiment. Similar results were obtained in an *in vitro* experiment using saline solution in the Behr reference (Example 13). Also, the Carson reference reports both CTL responses and humoral responses, which it attributes to the location of injection. There is no discussion whatever about how to target APCs, as opposed to other types of cells, specifically.

Furthermore, this 1994 reference can be placed in perspective by the discussion in the present specification at page 6, line 8 et seq., of Arthur, et al "A Comparison of gene transfer methods in human dendritic cells," Cancer Gene Therapy, v. 4, No. 1, 1997 pp 17-25[2], which reports that the then-known *in vitro* methods of gene transfer suffered from low efficiency. That article reported that, of a variety of gene transfer methods were tried for human DC, only adenoviral vectors were a promising vehicle for genetically engineering human DCs (Abstract). The application also discloses at page 6, line 14-19 that, as of 1998, "known *in vivo* methods include ... intradermal subcutaneous and intramuscular injection of DNA. None of these methods have been shown to effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into

[2] This reference has been of record in the present case, as acknowledged by the Examiner on 8/9/01. A copy of the reference is enclosed for the convenience of the Examiner.

the Langerhans cells."

The present Invention

The present application is a division of United States Patent No. 6,420,176, which was drawn to a novel DNA complex for gene delivery. The present application relates to a method of transfecting antigen presenting cells, the steps comprising
selecting a gene delivery complex that targets antigen presenting cells comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine, and polyethylenimine derivatives,
and applying the complex to the skin or mucosa surfaces of an animal,
wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter.

An advantage enjoyed by this invention is that the gene delivery complex need not be injected, but merely applied to the skin, according to the claimed method. The inventors have found, and the text of the application contains, experiments that demonstrate that both the wholly novel complex (DNA plus mannosylated PEI) and several other arguably disclosed complexes (DNA plus modified PEI, PEI with sugars, PEI alone, and sugars alone) also work in an elegant method for stimulating the immune system that does not rely on injection, added irritants or toxins, use of cultured cells or expensive new equipment such as a gene gun. The present application also discloses how to modify the teachings of the Behr reference so that the claimed antigen presenting cells can be targeted via the mannose receptor as opposed to the asialoglycoprotein receptor (at least at page 14, line 37 – page 15, line 15, and Example 6). These cells are disclosed to be capable of producing a CTL response (page 11, line 21) and proven to do so *in vitro* (Example 3), and *in vivo* (Example 4), and additional data submitted by the inventors shows that the immune response induced in this manner does not include antibody (humoral) responses using either the (injected) *ex vivo* or (applied to the skin) *in vivo* procedures. Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by Genetically Modified Dendritic Cells" J Virol, Aug 2001, p.7621- 7621-7628, at p 7626, lines 12-15, 1st full paragraph. See also Lisziewicz, et al., "DermaCir: A Novel Topical Vaccine for HIV/AIDS J Inv Dermatology, 2004, p. 6, col. 1, first paragraph, last 4 lines.

Analysis

To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." "Inherency, however, may not be

established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." (citations omitted) *In re Roberts*, 169 F.3d 743, 49 USPQ2d 1949 (1999). "We do not see how a disclosure or combination of disclosures leaving one to rely on fortune in choosing the referred to material can function as anticipation. Absent a showing of some reasonable certainty of inherency, the rejection under 35 USC 102 must fall." *In re Brink*, 419 F.2d 914, 918, 164 USPQ 247 (1970).

B. Examiner's Arguments

The Examiner has not pointed to any disclosure or discussion within the Behr reference relating to the claimed method, nor of any disclosure that would guide one of ordinary skill in the art to choose from the many options available, to make the claimed invention or obtain its advantages. The Examiner has relied, however, on two arguments in an effort to make the rejection.

1. Inherency – Luciferase as an Immunogen

The Examiner points to Example 14 of the Behr patent, where a plasmid encoding a marker gene for luciferase was diluted in 5% glucose solution to about 3% glucose, and then diluted with PEI and injected into the brains of newborn mice, whose brains were subsequently an assayed for light emission as a sign of transfection. The reference comments that this experiment shows the advantages of the compositions of that experiment for gene therapy, that the plasmid with PEI was transferred efficiently into the brain of mice, and that no significant luciferase activity was observed when the plasmid alone was used.

There is no disclosure or discussion of antigen presenting cells, no disclosure or discussion of how to specifically target antigen presenting cells as opposed to neurons, no experiment reporting an immune response, yet the Examiner argues without citation that Luciferase is inherently an immunogen, and that because the Behr reference taught elsewhere and without more, "topical application," that the Behr reference inherently teaches that the material in Example 14, *if placed on the skin* would target *antigen presenting cells*, because antigen presenting cells are in the skin. At best, this is an argument that it might have been obvious to try an experiment, and does not rise to the clear disclosure required to anticipate the claims.

The present application at page 6, lines 4-11 cites to a fairly contemporaneous reference (Arthur, et al.,) that indicates that different types of cell lines have different responses to transfection techniques and that of the methods screened, only adenoviral vectors showed promise for genetically engineering human DCs. (Abstract), and the application states that that the known techniques and materials had not been shown to

effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into the Langerhans cells. There is no reason to discredit this disclosure, especially in view of the Examiner's vigorous urging that the art at the time was unpredictable. Thus it is not clear that the unaltered material disclosed in Experiment 14 would inherently transfect antigen presenting cells.

It is not at all clear that luciferase will inherently cause an immune response. Luciferase is a commercially available reagent from, among many others, BD Biosciences, who characterize the material as follows on their web site:

http://www.bdbiosciences.com/pharmingen/products/display_product.php?keyID=76

Luciferase Reporter Assay Applied Reagents

> Since the firefly beetle (Photinus pyralis) luciferase gene was introduced to molecular biology, it has provided a method of utilizing biological light production as a tool for research. Luciferase interacts with its cognate substrate luciferin to produce light emission peaking at 562 nm. For use in the laboratory, this form of luminescence can yield a very sensitive non-radioactive assay. Firefly luciferase can be reliably expressed from various expression vectors and in a diversity of organisms as a reporter in studies of gene regulation. Luciferase reporter assay systems are currently one of the best **non-toxic**, rapid and sensitive methods to measure gene expression. The assay is based on the detection of luciferase activity which correlates with transcription due to DNA regulatory elements in genes, mutations within those elements as well as responses to extracellular and intracellular signals. (emphasis added)

CTL responses are cellular immune responses. For the purposes of gene therapy they are considered toxic because they result in the elimination of the cells expressing the DNA, which are considered to be the "cured" or "therapeutic" cells. (At minimum, elimination of the cured cells would result in elimination of the therapeutic and prophylactic benefit). That is why the Behr reference taught that immunogenicity is to be avoided in this context (Col. 1, line 51). If marker gene were used that resulted in a CTL response *in vivo*, the transfected cells might be destroyed fairly quickly, and the experiment might appear to fail. Thus a desirable marker gene is one that is likely to provoke little, if any, immune response, to avoid interfering with the tests.

It is noted that the Applicants have used a different marker gene in their experiments, a green fluorescent protein gene derived, it is believed, from jellyfish. Such a gene was used to produce a "GFP bunny," that is, a rabbit that glows in the dark, if stimulated by the proper light source. http://www.ekac.org/gfpbunny.html#gfpbunnyanchor If this marker gene inherently stimulated an immune response, assuming the animal could have been produced at all, the rabbit would have died from an autoimmune reaction shortly after it began to produce the protein. This existence of this genetically altered animal indicates that

not all marker genes are inherently cause immune responses, and so one of ordinary skill in the art would not read the experiment to show that the material disclosed in Example 14 would inherently cause an immune response.

2. Expectation of Success

Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). Both of these experiments rely on devices: intradermal injection of plasmid in saline solution (Example X, column 35, line48) or a tyne device (Col. 37, line 16). The "complex" as discussed above, is "naked" DNA, which was tested in the Behr reference and found ineffective.

Furthermore, this 1994 reference can be placed in perspective by the discussion in the application at page 6, first full paragraph, of Arthur, et al "A Comparison of gene transfer methods in human dendritic cells Cancer Gene Therapy, v. 4, No. 1, 1997 pp 17-25, which reports that the then-known *in vitro* methods of gene transfer suffered from low efficiency. The application also discloses at page 6, line 14-19 that, as of 1998, "known *in vivo* methods include ... intradermal subcutaneous and intramuscular injection of DNA. None of these methods have been shown to effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into the Langerhans cells." The Carson reference, which related to intradermal and intramuscular injection of DNA had not been shown to be effective.

C. Conclusion

The Behr reference does not disclose the claimed method because it does not indicate how to pick and choose among its teachings to transfect a different class of cells, dendritic cells, directed to what is for the Behr reference, a toxic response. Example 14 of the Behr reference does not include a material that one of ordinary skill in the art at the time the invention was made would interpret to inherently cause an immune response. The gene is a marker gene, and marker genes are selected for their low toxicity, one aspect of which is lack of tendency to produce immune responses. The Carson reference does not yield a reasonable expectation of success to an experiment abstracted from the Behr reference because subsequent publication and text in the present application disclose that the techniques used in the Carson reference had not been shown to yield sufficient efficiency of transfection in antigen presenting cells. This rejection is insupportable.

35 USC § 103

5. Obviousness

Claims 23-26, 28, 30-32, 35, 37-41 and 43 have been newly rejected under 35 U.S.C. 103(a) as being unpatentable over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Carson (US Patent 5,679,647) and in view of Holler (US Patent 5,908,923).

Parent application 60/058,933 (9-15-97) did not describe complexing DNA with a compound selected from the group consisting of sugars, PEI or PEI derivatives (claim 23). Parent application 09/153,198 (9-15-98) described complexing DNA with PEImannose in a 5-10% glucose solution on pg 26, lines 1-9; therefore, claim 23 has priority to 09/153,198 (9-15-98).

Behr is said to have taught a complex comprising i) PEI, and ii) plasmid DNA comprising a nucleic acid sequence encoding luciferase operatively linked to a promoter suspended in 5% glucose (Note: 3% or so. A 5% stock solution was diluted with two other solutions in a two-step process, therefore the end result is clearly not a 5% concentration of glucose.) (col. 12, lines 53-57). Luciferase is said to be an immunogenic protein because it is foreign to mammals and is alleged without citation to induce an immune response in mammals. Behr is said to have taught administering the complex to the skin or mucosa of an animal (claim 33, col. 6, lines 1-19). Behr is said to have taught the DNA could encode a peptide from HIV (col. 3, lines 57-67). The Examiner concludes that the method of Behr inherently results in transfecting APCs because dendritic cells. (*sic.* The sentence is taken to continue in the matter of the rejection above, "(a type of antigen presenting cell) are found in the epidermis (see difinition of "dendritic cell,"item 3)." Carson is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin transfects dendritic cells (col. 36-37, Examples 11-12). Case law established that reliance upon inherency in an obviousness rejection (103) instead of an anticipation rejection (102) is proper. *In re Skoner, et al.*, 186 USPQ 80 (CCPA). It is noted by the Examiner, however, that the phrase "transfecting antigen presenting cells" in the preamble does not bear patentable weight in considering the art because it may not occur.

Claims 25, 26 and 43 are said to be included because they are not limited to a compound that is mannosylated PEI or PEI "from a PEI 22 kDA;" claims 25, 26 and 43 encompass non-sugar-modified PEI solubilized in glucose as in parent claim 24.

Claims 28 and 30 are said to be included because Behr is said to have taught that between 5-20 equivalents of PEI amines are used relative to one DNA phosphate (col. 8, lines 15-19). The instant specification teaches that the ratio of 5:1 cause the complex to be electrostatically neutral, (T bridging pg 21-22).

Claim 33 has been excluded because 5% is not "8%" as newly amended.

Claims 35 and 41 are said to be included because administering the complex to the skin/mucosa as taught by Behr inherently would activate APCs by toxin activation. Cells would start expressing luciferase and this firefly "toxin" would be recognized as foreign by the animal, thereby activating APCs, including Langerhans cells.

The Examiner admits that the Behr reference did not teach using a plasmid encoding a protein from a replication-defective, integrase-defective HIV. However, the Holler reference is said to have taught a plasmid encoding a replication-defective HIV that was integrase defective for use in vivo (col. 4, lines 51-54).

Thus, the Examiner states that it would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a gene delivery complex comprising a plasmid encoding an HIV protein to the skin/mucosa of an animal as described by Behr, wherein the plasmid encoded a replication-defective, integrase-defective HIV as taught by Holler. The Examiner states that one of ordinary skill in the art would have been motivated to make the HIV replication-defective and integrase-defective to prevent causing disease in the animal.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin,* 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this case, the desire to replace luciferase protein with an HIV protein was expressly taught by Behr. The desire to replace a plasmid encoding "an HIV peptide" taught by Behr with the plasmid encoding the replication-defective, integrase-defective HIV taught by Holler would not require hindsight reasoning. One of ordinary skill in 1997 would have recognized that an attenuated HIV such as the one described by Holler would prevent viral replication and death of the animal. One of ordinary skill in the art would have also recognized that attenuated HIV was desirable in a lab setting to add an extra measure of safety for lab technicians in case of accidental exposure.

Applicants argue the examiner "refuses to give patentable weight to the phrase "transfecting antigen presenting cells" (pg 21). Applicants' argument is moot. The examiner provided reasoning why the method of Behr inherently results in transfecting APCs as claimed and case law that states that relying on inherency in an obviousness rejection is acceptable.

Applicants argue the examiner has merely pieced together the references to come up with motivation to experiment. Applicants' argument is not persuasive. The examiner has provided a specific plasmid encoding a replication-defective, integrase-defective HIV for use in the method of Behr and motivation for why one of ordinary skill would want to do so. "Motivation to experiment" is a mischaracterization of the motivational statements provided by the examiner; the motivational statement provided by the examiner is based on the desire to prevent HIV infection or death of the animal receiving or applying the gene delivery complex. Holler provides evidence for the desire to use a replication-defective, integrase-defective HIV to induce an immune response in an animal without causing infection or death.

Applicants argue Holler merely teaches that the replication-defective, integrasedefective HIV is usable in vivo but did not expressly use the HIV in vivo. Applicants' argument is not persuasive. Neither Behr nor Holler needs to provide examples of using the virus in vivo. Behr is being relied upon for the step of applying a plasmid encoding an HIV protein to the skin of an animal.

Applicants' argument in the paragraph bridging pg 26-27 appears to relate to the expectation of success. It appears that applicants are attempting to point out that some HIV vectors are "inefficient" at transfection. Applicants' arguments are not persuasive. First, transfecting inefficiently is still transfecting. Inefficient rates of transfection would not deter someone from using an HIV vector that prevents infection or death of the animal receiving or applying the gene delivery complex. Aurthur (Cancer Gene Res., 1997, Vol. 4, No. 1, pg 17-21) has not been considered because it has not been provided. Second, the combined teachings of Behr and Holler provide a reasonable expectation of successfully transfecting cells because Holler transfected CEM (a lymphoblastoid cell line) with integrase-defective

HIV. Therefore, one of ordinary skill in the art at the time the invention was made would still have a reasonable expectation of successfully transfecting APCs using a plasmid encoding the HIV taught by Holler.

In response to applicants arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

5. Response – Obviousness

A. Applicable Law

Applicants note that they have distinguished over the withdrawn obviousness rejection using the classic obviousness analysis in the classic format, that is, by describing the claimed invention, determining the scope and content of the prior art, comparing the prior art to the presently claimed invention, and presenting analysis explaining why it would not have been obvious to one of ordinary skill in the art to make the claimed invention (not just run an experiment) at the time of the invention.

Counsel's use of headers to break up an extended piece of writing does not convert this analysis to a piecemeal attack on the references individually. This is the analysis required both by the supervisory court, and by the agency's own instructions. This legal background has been made of record, and it is included here for the convenience of the Examiner and to confirm that the MPEP instructions are in accord with the Court's case law.

Whether patents are allowable in a given particular field of art is not a question of Patent and Trademark Office discretion but of law, and examiners have no discretion to deny patents to inventions meeting the statutory criteria. *Animal Legal Defense Fund v. Quigg*, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985).

Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. The four factual inquires enunciated therein as a background for determining obviousness are as follows:

(A)Determining the scope and contents of the prior art;

(B)Ascertaining the differences between the prior art and the claims in issue;

(C)Resolving the level of ordinary skill in the pertinent art; and

(D)Evaluating evidence of secondary considerations. (MPEP 2141)

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art combination must teach or suggest all the claim limitations. The

teaching or suggestion to make the claimed combination and the expectation of success must be both found in the prior art, not in the applicant's disclosure. MPEP 2143. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1071, 5 USPQQ2d 1596 (Fed. Cir. 1988).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)

If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) If the proposed modifications or combination of the prior art would changed the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); see also MPEP 2143.01

B. Factual Background: The Claimed Invention, the Scope and Content of the Prior Art, the Differences between the Claimed Invention and the Prior Art

The Behr Reference

The Behr reference relates to the use of PEI as an adjuvant for gene therapy (Abstract), preferably in conjunction with plasmid DNA, although a wide variety of other materials are disclosed as well. Gene therapy is disclosed to consist in correcting a deficiency or an abnormality (mutation, aberrant expression, and the like) or in effecting the expression of a protein of therapeutic value by introducing genetic information into the affected cell or organ (Col. 1, lines 11-15). Gene therapy is a field distinct from the subject matter of the present invention, which is immunotherapy, and this reference discloses that immunogenicity is to be avoided in this context (Col. 1, line 51).

The reference states that PEI can be used in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), in a wide variety of configurations, including a wide range of amine to phosphate mol ratios (0.5 – 50 at Col. 2, line 50) without any distinction as to what might be accomplished by varying such ratios, using a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57; sugars are listed as useful for targeting the asialoglycoprotein receptors at Col 5, lines 64-65), for a wide variety of purposes (for example, the production of therapeutic products including enzymes, blood derivatives, hormones, lymphokines,...growth factors, neurotransmitters...synthetic enzymes, etc,, -- a list that includes thousands of items. See Col. 3, lines 29-44. Antigenic peptides are also listed at Col. 3, line 57-67, as well as antisense genes (Col. 3, line 45), sequences (Col. 4, line 1, and upstream signals to control therapeutic genes (Col. 4, lines 25-29) and that it can be used in formulations with a view to topic, cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like (Col. 6, lines 1-4) in formulations that that might be isotonic sterile solutions, dry, water or saline (Col. 6, lines 9-12 as appropriate *to enable injectable solutions to be formed* (line 13, emphasis added). Both saline (Example 13 and glucose Example 14) formulations are disclosed, without any distinction as to any advantage that might be obtained. Both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), but only direct injection into the brain for the transfection of neural tissue is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration, or any disclosure whatever of the transfection of antigen presenting cells, or the provocation of any type of an immune response.

This reference has disclosure consistent with that for a new material or a new use for a material with potentially wide application in a given field. What is beyond the scope of this reference is specific instruction as to how to realize the full potential of the material, that is, how to obtain the results that are potentially available from it, in areas that were not of direct interest to the inventors of the reference at the time. The Examiner's statement, that the Behr reference is relied upon for the step of applying a plasmid encoding an HIV protein to the skin of an animal, is ineffective because the Behr reference shows no such thing.

The Carson Reference

The Carson reference is said to provide evidence for the examiner's assertion of inherency by teaching a gene delivery complex applied to the skin that transfects dendritic cells (col. 36-37, Examples 11-12). The definition of the complex is apparently plasmid DNA only, and is referred to repeatedly as "naked" e.g., Col. 30, line 41. These materials were formulated in saline solution (Col. 31, line 18). Both of the cited experiments rely on devices: intradermal injection of plasmid (Example X, column 35, line48) or a tyne device (Col. 37, line 16). Naked DNA formulated in a glucose solution was tested in the Behr reference Example 14, Col. 13, lines 9-10, injected and found not to work in that experiment. Similar results were obtained in an in vitro experiment using saline solution in the Behr reference at Example 13, Col. 12, lines 39-41). Also, the Carson reference reports both antibody responses (Col. 31, lines 54-56) and CTL responses (Example IX) which it attributes to the location of injection, intradermal rather than intramuscular. There is no discussion whatever about topical application, or how to target APCs according to the manner of the claimed invention. Further, it is noted that the later, Behr reference discussed above, tested the materials and methods of the Carson reference and found them ineffective, at least for the transfection of brain cells.

The Holler Reference

USPN 5,908,923 to Holler, et al. discloses and claims a sequence listing for a specific transdominant negative integrase gene which is said to be capable of making at least one cell resistant to a retroviral infection. This gene was used *in vitro* to transfect a lymphoblastoid cell line. The Examiner admits that this reference does not disclose any *in vivo* method.

The methods of transfection mentioned are calcium phosphate co-precipitation, cationic liposomes, electroporation, receptor mediated endocytosis, naked DNA, transduction by viral vector, and particle-mediated gene transfer. The only method discussed, (which is also shown in the Examples) is calcium precipitation.

This disclosure simply amounts to a suggestion that the gene is useable. It says nothing about the claimed method. Indeed, this 1994 reference would appear to recommend that the gene can be successfully delivered by any and all methods. See Col. 7 lines 40-57. However, the present application discloses that an article published several years later compared transfection rates in antigen presenting cells and a cancer cell line (melanoma) that was known to be readily transfected by all the methods tested. (page 21, lines 2-4). This article reported only "low efficient" *in vitro* methods were known at the time, see page 6, lines 4-11 (cite to Arthur, J. F. et al., Cancer Gene Therapy 4:1 17-21, 1997 and Song, E. S., et al., PNAS USA 94:5, 1943-8, 1997[3]); and that neither they nor the known *in vivo* methods had been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin into the Langerhans cells. See page 6, lines 16-19. Thus, this reference adds nothing to the cited combination.

The Examiner has stated that the applicants' comment that the Holler reference recommends the gene can be successfully delivered by any method, and that this is not persuasive because certain "low efficient" methods cited in the background section of the present application were said to be "successful." First, the application text discloses that these experiments were not successful. The application discloses that they had not been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin. Further, the reference does not teach the claimed method, and it is the method, not the raw materials, that is lacking in the prior art. Christening the prior art "successful" doesn't change the fact that the new method is not disclosed in the prior art. The reference does not differentiate among types of cells, methods of gene delivery, or provide any basis to choose the present method from among many, successful or not. The claimed invention is not a given retrovirus, nor is it an adjuvant. It is a method of transfecting antigen presenting cells.

The Claimed Invention

A method of transfecting antigen-presenting cells, the steps comprising selecting a gene delivery complex that targets antigen presenting cells, comprising DNA and one or more compounds selected from the group consisting of sugars, polyethylenimine,

[3] This reference has been of record in the present case, as acknowledged by the Examiner on 8/9/01. A copy of the reference is enclosed for the convenience of the Examiner.

and polyethylenimine derivatives, and applying the complex to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter.

An advantage enjoyed by this invention is that the gene delivery complex need not be injected, but merely applied to the skin, according to the claimed method. The inventors have found, and the text of the application contains, experiments that demonstrate that both the wholly novel complex (DNA plus mannosylated PEI) and several other arguably previously disclosed complexes (DNA plus modified PEI, PEI with sugars, PEI alone, and sugars alone) also work in an elegant method for stimulating the immune system that does not rely on injection, added irritants or toxins, use of cultured cells or expensive new equipment such as a gene gun.

Differences between the Claimed Invention and the Prior Art

Among the differences between the presently claimed invention and the primary reference (Behr) are that the reference does not disclose the transfection of, or targeting of, antigen presenting cells, a most significant subset of cells, and prominent by its omission, or formulations that can be used for needleless, *in vivo* delivery of genes into any cells, much less antigen presenting cells, or any *in vivo* method of delivery except injection. The reference does not teach or suggest the use of sugars to target the mannose receptor, the significance of having an electrostatically neutral complex in this context, the significance to the inventors' method of the ratio of nitrogen to phosphate, use of glucose solutions in the claimed range, any reason to prefer a glucose solution over a saline solution, or any further steps to enhance the response of the skin to the formulation. The other references do not supply any of the missing information.

The present application discloses how to modify the teachings of the Behr reference so that that the claimed method targets antigen presenting cells instead of neurons (at least at page 14, line 37 – page 15, line 15, and Example 6), in part by using a specific type of formulation based on multiple factors including the use of sugar-modified formulations and manipulation of a nitrogen/phosphate mol ratio to target a different receptor from that suggested by the Behr reference, and in part by refraining from using any injection method, that is, placing the formulation on the skin. The transfected APC are capable of producing a CTL response (page 11, line 21), which is toxic for the purposes of the Behr reference (Col. 1, line 51), Additional data submitted by the inventors shows that the immune response induced in this manner does not include antibody (humoral) responses using either the (injected) *ex vivo* or (applied to the skin) *in vivo* procedures. Lisziewicz, et al., "Induction of Potent Human Immunodeficiency Virus Type 1-Specific T-Cell-Restricted Immunity by

Genetically Modified Dendritic Cells" J Virol, Aug 2001, p. 7621-7628, at p 7626, lines 12-15, 1st full paragraph. See also Lisziewicz, et al., "DermaVir: A Novel Topical Vaccine for HIV/AIDS J Inv Dermatology, 2004, p. 6, col. 1, first paragraph, last 4 lines, and second paragraph, lines 2-4.

Analysis

The present rejection does not establish a *prima facie* case of obviousness against the amended claims because the claimed method is not present in any of the references individually, or their combination. As discussed in more detail in the 35 USC § 102 rejection above, the Behr reference does not inherently disclose the claimed method, with or without the support of the Carson reference. The Behr reference must be modified in order to derive the claimed invention. The present application discloses how to modify the teachings of the Behr reference so that that the claimed method targets antigen presenting cells (a different class of cells from neurons) (at least at page 14, line 37 – page 15, line 15, and Example 6), which are capable of producing a CTL response (page 11, line 21), which is toxic for the purposes of the Behr reference (Col. 1, line 51), in part by using a specific type of formulation to target a different receptor from that suggested by the Behr reference, and in part by refraining from using any injection method, that is, by placing the formulation on the skin.

The question presented here, therefore, is whether the cited references contain teachings sufficient for one of ordinary skill in the art to conclude the proposed modifications would work, without rendering the Behr reference inoperative.

The Carson reference is said to teach a gene delivery complex applied to the skin that transfects dendritic cells. This is not strictly true, for the "complex" is just plasmid DNA, and both of the experiments relied upon by the Examiner use injection devices. Further, plasmid DNA alone, in both saline (Experiment 13) and glucose solution (Experiment 14) was used in the Behr reference and found to be ineffective. And the Applicants have submitted evidence that, by the time the present invention was made, it had become known that different types of cells had different sensitivities to transfection, so that the older reference would not be considered by one of ordinary skill in the art to assure success with another. See Arthur, et al "A Comparison of gene transfer methods in human dendritic cells" Cancer Gene Therapy, v. 4, No. 1, 1997 pp 17-25[4], which reports that the then-known *in vitro* methods of gene transfer suffered from low efficiency. The application also discloses at page 6, line 14-19 that, as of 1998, "known *in vivo* methods include ...

[4] This reference has been of record in the present case, as acknowledged by the Examiner on 8/9/01. A copy of the reference is enclosed for the convenience of the Examiner.

intradermal subcutaneous and intramuscular injection of DNA. None of these methods have been shown to effectively deliver genes into antigen presenting cells, such as dendritic cells, much less delivery of genes through the skin into the Langerhans cells." See also the Pollard reference discussed at page 15, lines 3-6. [5] One of the conclusions drawn by the authors of that 1998 article was that barriers to gene transfer vary with cell type (Abstract, and p. 7510, col. 2, last full para, lines 1-8 UP). This disclosure is especially credible in light of the Examiner's vigorous insistence, in another context, that the art was at the time unpredictable. Thus the Carson reference is only useful as a disclosure of a raw material that has not yet been made to work.

The Examiner does not assert that the Holler reference teaches anything about the claimed method, only that it teaches the existence of a plasmid encoding a replication-defective, integrase defective HIV. Assuming the raw material is as described, there is still no description of the claimed method.

Neither the secondary nor tertiary reference, nor their combination, present any modification to the base reference, other than to suggest raw materials. They have nothing to add to the claimed method. The *prima facie* case for obviousness has not been made, and this rejection must be withdrawn.

Secondary Considerations – Objective Evidence of Non-Obviousness

Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present.

A vaccine according to the currently claimed invention is in human clinical trials in two countries. It is noted that clinical trial results are expressly NOT required according to the MPEP, however, the MPEP also acknowledges that "Before a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. MPEP 2107.02. It is respectfully submitted that acceptance for human clinical trial is not only evidence of the asserted therapeutic utility, but also some objective evidence of nonobviousness.

A statement listing the trials can be found at
http://www.geneticimmunity.com/pages/906725/index.htm
In the event a Declaration to this effect is desired, the applicant will supply same.

---

[5] This reference has been of record in the present case, as acknowledged by the Examiner on 8/9/01. A copy of the reference is enclosed for the convenience of the Examiner.

Note: Examiner's Contention – Antigen Presenting Cells

Claim 23 has been amended so that the complex must target antigen presenting cells. This limitation must now be given patentable weight. The Examiner states without offering any rationale that "transfecting antigen presenting cells" "may not occur." The applicants have pointed out that the evidence that "transfecting antigen presenting cells" has occurred is in the text of this case and is copious. With the claims amended so that the limitation is in the body of Claim 23, this limitation must be considered. MPEP 707.07(l).

Examples in the application present evidence that APCs were indeed transfected. They were transfected *in vitro* using the best available prior art material for antigen presenting cells, lipofectamine (Example 1, plasmid DNA encoding HIV-1/LWint-, an integration and replication defective HIV described in one of the inventors' other applications, showing production of various proteins; Example 3 demonstrates that these cells developed the desired CTL response *in vitro*). They were transfected *in vitro* using PEI, showing that PEI worked better than lipofectamine, in Example 5. The PEI-transfected cells were shown to produce an *in vivo* CTL immune response in Example 4.

DC were transfected with a plasmid encoding green fluorescent protein and a variety of other adjuncts *in vitro*, including various PEI derivatives (Example 6).

Antigen presenting cells were transfected according to the method in Example 8, using a plasmid encoding green fluorescen protein where the claimed complexes were applied to the skin of mice (page 22, line 37) and then skin samples were tested for transduction of Langerhans cells, and it was found that a sugar modified gene delivery system is preferred to transduce antigen presenting cells. (page 23, lines 19-20). Example 9 shows that the claimed complexes also migrated to the lymph nodes and expressed protein (page 24, lines 6-7).

Note: Motivation

The Examiner's citation of the Holler reference for a desire to use attenuated HIV as a raw material for vaccines does not supply the teaching needed to derive the claimed method. Further, the cells that were transfected were cancer (lymphoblastoid) cells in vitro, by electroporation. It says nothing about transfection of antigen presenting cells *in vivo*, by spreading a formulation on the skin. Given the disclosure in the present application, and in the references cited therein, that such methods of transfection were not effective, and that barriers to gene transfer vary with cell type, this reference cannot be said to supply either the kind of specific teaching or the expectation of success required to support an obviousness rejection.

C. Conclusion

In view of the above analysis and the evidence, it is respectfully submitted that the present rejection is inapplicable to the amended claims because neither the individual references nor their combination yield the claimed invention, and the case is well-supported by experimental results and secondary considerations.

Conclusion

For all the above reasons and amendments, it is believed that all the Examiner's legitimate concerns have been fairly met. Favorable consideration is solicited.

Respectfully Submitted,

Valerie E. Looper
Registration No. 33,007

The Law Offices of
Valerie E. Looper
11726 Lightfall Court
Columbia, Maryland 21044
Telephone: (410) 715 - 5771
fax: (410) 715-5771